The Medicine Cabinet: Pregabalin

Judy Longworth

Senior Clinical Pharmacist and Psychiatrist, Department of Psychological Medicine, The Children's Hospital at Westmead

Pregabalin is an antiepileptic drug also used for chronic pain especially neuropathic pain i.e. pain from nerves and anxiety. Pregabalin is a gabapentoid which is a structural analogue of GABA (gamma aminobutyric acid) but does not act on GABA receptors or alter GABA metabolism of reuptake. It was developed by Pfizer Pharmaceuticals. Pregabalin works by blocking the alpha -2 delta calcium channels which has a presynaptic modulatory effect over the excitatory neurons and, similar to benzodiazepines, this is expected to occur rapidly. Pregabalin does not act as an antagonist at glutamate and has no effects on serotonin reuptake. This action is similar to gabapentin but better absorbed at higher doses. Pregabalin was approved by TGA in 2005 for treatment of neuropathic pain in adults and as adjuvant therapy for adultepileptics and on the PBS from 2013 for neuropathic pain. In Europe, the European Medicines Authority has licensed pregabalin as an anxiolytic in adults. There is some evidence for its use as anxiolytic in children and adolescents.

Dosing from the various adult clinical trials indicate that dosing start at 150mg/day administered in two to three divided doses and then increase to 300mg/day within 3-7 days and increase further in 1 week until maximum dose is achieved. Maximum dose varies depending on the condition, the domain for pain doses can range from 300mg-600mg/day and generalised anxiety maximum dose is 600mg/day. The dose should be weaned over a minimum of 1 week when discontinuing. Withdrawal symptoms include insomnia, headache, anxiety, diarrhoea, flu syndrome, nervousness, pain, convulsions hyperhidrosis and dizziness may occur (Lyseng-williamson, 2014).

Pregabalin pharmacokinetic profile is;	
Time to maximum plasma concentration	1hour
Time to steady state	24-48 hours
Metabolism	negligible
Plasma elimination half-life	6.3hours

Drug interactions	
Pharmacokinetic	no hepatic or induction or inhibition of CYP enzymes
Pharmacodynamic	additive somnolence and sedation, cognitive and gross motor function impairment with CNS depressants
	Additive constipation with opioids
	Lower gastrointestinal function

Adverse effects

Clinical trials have identified many adverse effects, some are present initially but others may have long term effects and all should be reported to the prescriber. Weight gain as well as dizziness and somnolence were reported especially initially. Other adverse effects include fatigue, blurred vision including diplopia, dry mouth, headache and unsteadiness, oedema and peripheral swelling, lethargy, confusional state, memory impairment, nausea, diarrhoea and constipation. Other reported adverse effects include coordination problems such as abnormal gait, vertigo and balance problems,

Anxiety clinical trials

A meta-analysis published by Generoso et al in 2017 compares eight studies (n=2299patients) with a mean age of 42.38 years (range 35.6-72.3 years) with 61.6% women with pregabalin administered as the only pharmacological intervention. Primary outcome of the study showed that pregabalin was significantly superior to placebo (Generoso, 2017). There is limited long term studies identified but there was a fast onset of clinical improvement. A sub analysis including a trial of pregabalin vs benzodiazepines showed a lower dropout rate than benzodiazepines and comparable clinical response.

Montgomery *et al* looked at the efficacy of pregabalin in anxiety and concluded that using pooled analysis and modelling that when a reduction in the HAM-A (Hamilton Anxiety Rating Scale used to rate the severity of a patient's anxiety) of 20% or more from baseline at week 2 were predictive of a response at endpoint (Montgomery et al, 2017). Although at doses of 150mg/day were less effective than higher doses there is no notable dose response for any dose more than or equal to 200mg/day. Treatment guidelines and prescribing information recommend doses between 150mg to 600mg/day. The frequent adverse events include somnolence and dizziness as well as dry mouth and incoordination which appear to be dose related.

Boschen also did a meta-analysis of 7 randomised controlled trials in 2011 and showed that pregabalin has a greater effect on the psychic anxiety symptoms as identified in the HAM-A compared to the somatic anxiety symptoms (physical manifestations). The psychic anxiety symptoms include mental agitation and psychological distress. The overall effect was a significant advantage over placebo but size of the effect was only moderate (Boschen, 2011).

There is an overall lack of clinical trials comparing pregabalin to other forms of pharmacotherapy for anxiety (Lyseng-Williamson, 2014).

Neuropathic pain and Fibromyalgia trials

These conditions with generalised anxiety disorder are common, chronic and complex and associated with significant quality of life issues, Pregabalin has shown efficacy in the treatment of post-herpetic neuralgia and neuropathic pain associated with diabetic peripheral neuropathy and spinal cord injury in adult randomised double-blind placebo controlled trials in adult patients. The overall health status of patients improved with pregabalin compared to placebo. Sleep has also been shown to improve in these patients (Lyseng-Williamson, 2014).

> "The overall health status of patients improved with pregabalin compared to placebo"

Adolescent and children trials

In a recent review of gabapentin and pregabalin safety and efficacy in pain by Egunsola *et al* there were 7 publications identified for qualitative synthesis. Although there are extensive studies in adults there is a paucity of good randomised controlled trials in pain management for children and adolescents. Problems in identifying self-reported pain measures ensure that a meta-analysis of results is impossible. The side effects reported in these trials include nausea for gabapentin and dizziness for pregabalin being the most common (Egunsola *et al*, 2019).

Antinew *et al,* reports in this pharmaceutical company trial with comparative dosing of 2.5mg/kg/d or 10mg/kg/d and placebo doses. Previous study evaluated the safety, tolerability and pharmacokinetics of pregabalin in children (N=65) with partial seizures, 1 month to 16 years. Although doses of 2.5mg/kg/d achieved a reduction in the seizure rate as measured on a 28 day seizure rate, it was not significant when compared to placebo but 10mg/kg/d was significant (Antinew *et al*, 2019).

In burns patients, pruritus is often indistinguishable from neuropathic pain, a review of use of gabapentin and pregabalin resulted in a chart review of 136 patients. These patients had previously failed to control the itch with diphenhydramine or hydroxyzine. If gabapentin failed to relieve the itch then pregabalin is added. Minimum effective dose for pregabalin taken together with gabapentin for 6-12 years was 6.5$\pm$3.5mg/kg/d and 4.7$\pm$1.6mg/kg/d for >12 years. The combination was well tolerated and reports of 88.2% response neuropathic pain and pruritus and 100% response for pruritus alone. Although the combination was well tolerated, one patient reported excessive sedation and another nausea, vomiting, and headaches which ceased on withdrawal of gabapentin (Kaul *et al*, 2018).

Post marketing surveillance has shown an increase in

suicidally and suicidal ideation amongst people taking pregabalin for pain and epilepsy. Thus, people taking it should be monitored and if suicidal, refer back to the treating team or seek other medical advice through GP or ED.

There has also been an increase in the use of pregabalin illegally via the illicit drug market and thus concern about diversion of products that are legitimately prescribed so ensure any medications are stored properly. Pregabalin misuse is for higher doses for its euphoric effects and thus physical dependence has been reported. This problem has been illustrated in the media and there are reports that in Europe pregabalin and gabapentin now have restrictions on the prescriptions and are being classified as controlled substances.

References:

Antinew, J., Pitrosky, B., Knapp, L., Almas, M., Pitman, V., Liu, J., Craiu, D., Modequillo, M., Nordi, D., Farkas, V. and Farkas, M.K. (2019). Pregabalin as adjunctive treatment for focal onset seizures in pediatric patients: a randomized controlled trial. *Journal of Child Neurology.* 34:5, 248-255.

Boschen, M.J. (2011). A meta analysis of efficacy of pregabalin in the treatment of generalised anxiety disorder. Canadian *Journal Of Psychiatry.*56:9, 558-566.

Egunsola, O., Wylie, C.E., Chitty, K.M. and Buckley, N.A. (2019). Systematic review of the efficacy and safety of gabapentin and pregabalin for pain in children and adolescents. *Anesthesia-Analgesia.*128:811-9.

Generoso, M.B., Trevizol, A.P., Kasper, S., Cho, H.J,. Cordeiro, Q. and Shiozawa, P. (2017). Pregabalin for generalized anxiety disorder: an updated systematic review and meta analysis. *International Clinical Psychopharmacology.* 32: 49-55.

Kaul, I., Amin, A., Rosenberg, M., Rosenberg, L. and Meyer, W.J. (2018). Use of gabapentin and pregabalin for pruritus and neuropathic pain associated with major burn injury: a retrospective chart review. *Burns.* 44; 414-422.

Lyseng-Williamson, K.A. (2014). Pregabalin: a guide to its use in fibromyalgia, neuropathic pain and generalised anxiety disorder. *Drugs Therapeutic Perspective.* 30:75-84.

Montgomery, S.A, Lyndon, G., Almas, M., Whalen, E. and Prieto, R. (2017). Early improvement with pregabalin predicts endpoint response in patients with generalised anxiety disorder: an integrated and predictive data analysis. *International Clinical Psychopharmacology.* 32: 41-48.

Further Reading:

Cairns, R., Schaffer, A.L., Ryan, N., Pearson, S. and Buckley, N.A. (2018). Rising Pregabalin use and misuse in Australia; trends in utilization and intentional poisonings. *Addiction*. 114;6.